

Appl. No. 09/719,867
Arndt. dated June 13, 2006
Reply to Office Action of February 13, 2006

REMARKS

Claims 1, 3-6, 8-14, and 16-36 are currently pending in the present case. Claims 3 and 25 to 35 have been withdrawn as directed to a non-elected invention. Claims 1, 4-6, 8-14, 16-24 and 36 are rejected; claims 5, 6, 9-14, 22-24 and 36 are objected to. Claim 1 has been cancelled. All claims previously dependent on claim 1 have been amended to be dependent on newly added claim 37. No new matter has been added.

Perfection of the Priority Claim to Provisional Application

In the office action mailed February 13, 2006, the Examiner notes that the priority claim must be perfected in compliance with 37 CFR 1.78(a) to claim priority to the provisional application 60/105,965 filed 28 October 1998 by submitting an amendment to the first paragraph of the specification claiming priority to the provisional application under 35 U.S.C. 119(e) and the International Application PCT/US99/22118, filed 23 September 1999 under 35 U.S.C. 120. Since the reference to the prior application was previously submitted on the Declaration as filed in the national application within the time limit set forth in 37 CFR 1.78(a), but not in the first sentence of the specification or application data sheet (see Declaration), and the priority claim was recognized on the filing receipt of the instant application (a copy of which is enclosed), Applicants believe that submission of the amendment of the first paragraph of the specification as is provided in this response is sufficient to perfect the priority claim. Applicants respectfully request early notice to this effect.

Absence of Abstract

The Examiner has requested that the applicants provide an abstract of the disclosure. Applicants have complied with this request by providing a copy of page 35 that was submitted with the application as filed (see the PCT published application which contains the Abstract). Applicants respectfully request that this objection to lack of an abstract be withdrawn.

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Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1, 4-6, 8-14, 16-24 and 36 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. This rejection is respectfully traversed.

Claim 1 has been cancelled and replaced with claim 37 in which the Examiner's 112 rejections have been corrected.

Claims 1, 4-6, 8-14, 16-24 and 36 are deemed indefinite because of the use of the plural term "mutations" in the preambles of each independent claims 1, 5, and 6 while the singular term "mutation" is indicated in the final steps of each of claims 1, 5, and 6. Claims 5 and 6 have been amended to clarify that the process is capable of "identifying one or more mutations" which then comports in plurality with the singular "mutation" in the final step of claims 5 and 6.

Claims 1, 4, 8, 16-21 and 36 are deemed indefinite because of the use of the term "defined set" in claim 1 (step a). The examiner alleges that neither the specification nor the prior art provide a definition of the term and it is not clear what properties might distinguish a "defined set" of PCR products from any other set of PCR products. Applicants have cancelled claim 1 and added new claim 37 to address the 112 issues asserted against claim 1.

Claims 1, 4, 8, 16-21 and 36 are deemed indefinite because of the use of the term "which encompass the complete chromosome of a wild-type strain bacteria for which the chromosomal sequence is known" in step a of claim 1. The examiner questions whether this phrase refers back to the "defined set of overlapping PCR products" or modifies the term "random point mutations". The Examiner asserts that the claims as written are vague and indefinite. Claim 37 makes it clear that the phrase "defined set of overlapping

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PCR products" refers to the overlapping PCR products, not the "random point mutations".

Claims 1, 4, 8, 16-21 and 36 are deemed indefinite because of the use of the limitation "the PCR product from a resistant strain identified in step (c)" in step (d) of claim 1 lacks sufficient antecedent basis. Claim 37 has been provided clear antecedent basis for the phrase.

Claim 4, drawn to the process according to claim 1 for identifying and characterizing drug-target interactions, is indefinite as the examiner does not understand how the claim further limits claim 1 which is drawn to a method for identifying mutations when the text of claim 4 does not indicate how claim 1 can be further modified to result in the "identifying and characterizing" of drug-target interactions.

Claims 5, 9-14 and 36 are indefinite in failing to relate the various steps of claim 5 to achieving the objective of "identifying and characterizing mutations that confer resistance to a compound."

Claim 9 is indefinite over the recitation of the limitation of "the bacteria" in line 1 whereas each of claims 5 and 6 recite multiple types of "bacteria". The claim has been amended to clearly point to "said" bacteria of claims 5 and 6.

Claims 6, 9, 22-24, and 36 are indefinite in failing to relate the various steps of claim 6 to achieving the objective of "identifying mutations that confer resistance to a compound." Applicants traverse the rejection and request reconsideration. Means for identifying mutations that confer resistance to a compound are taught in the specification. One of skill in the art would know how to identify mutation.

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Claims 22-24 are indefinite in failing to define how these claims further limit claim 6 relate to one another in achieving the objective of "identifying and characterizing mutations that confer resistance to a compound."

In view of these amendments and remarks, withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

The above discussion and corresponding amendments are based on section 112 issues and are not made to overcome art-based rejections. Accordingly, such discussion and corresponding amendments should not be construed in a limiting manner.

Rejection Under 35 U.S.C. §103

The examiner has rejected claims 5-6, 9, 22, 24 and 36 as being unpatentable under 35 U.S.C. §103 as allegedly obvious in light of over Kok et al. (Journal of Bacteriology, July 1997, pp 4270-4276, Vol. 179, No.13) in combination with Minshull et al. (US Patent No. 5,837,458 [11/1998]; filed 5/1996); or the forgoing combination taken together with either Belland et al. (Molecular Microbiology 14(2):371-382 [1994]), Pruna (U.S. Patent No. 5,532,239 [7/1996]), Ibrahim et al (U.S. Patent No. 5,145,667 [9/1992]) or Wohlstader (US. Patent No. 6,087,177 [7/11/2000; filed 3/16/1992]). These rejections are respectfully traversed. Applicants note that in previous office actions Kok et al. in combination with Belland was applied to allege that the same claims were obvious. The Examiner has essentially applied Minshull in place of Belland and asserted the same rejections. Applicants reassert all of the arguments previously asserted in the responses to the prior office actions.

Applicants will address the numbered paragraphs in the Office action in order to simplify the reading of this response.

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(12) The Examiner has rejected Claims 5-6, 9, 22, 24 and 36 as being unpatentable over Kok et al. in view of Minshull et al.

The Examiner states that "Kok et al. teach a method in which the procedures of PCR mutagenesis and transformation of PCR products into cells are combined to prepare and identify novel gene variants encoding proteins with functional properties of interest." The Examiner further states that "Kok et al teach that their method allows for the "swift assessment and convenient analysis of a wide range of mutations caused by errors introduced by PCR."

The Examiner acknowledges that Kok et al. do not teach the use of their method in the identification of mutations that confer resistance to a compound; with specific reference to claim 5, Kok et al. "do not teach the generation of PCR products meeting the length requirement of the claims which 'encompass the complete chromosome' of a 'wild-type bacteria strain for which the chromosomal sequence is known', and the incorporation of said product into the chromosome of a 'wild-type bacteria.' " In addition with specific reference to claim 6, the Examiner acknowledges that "Kok et al. do not teach the generation of PCR products meeting the length requirement of the claims 'which encompass the complete chromosome' of a 'strain of bacteria which demonstrates resistance to a compound,' and the incorporation of said product into the chromosome of a 'wild-type bacteria.' "

Kok et al. describe a PCR-based technique for targeted random mutagenesis of selected genes in a bacterial chromosome (Abstract, line 1, emphasis added and p 4275, paragraph 4 of the Discussion section) in order to gain insight into how structure influences the function of the protein encoded by the selected gene. Specifically Kok discloses only mutagenesis of *Acinetobacter pobR* which encodes the transcriptional activator of *pobA*, using a 1434 bp region containing *pobR* as a template. Kok discloses that PCR-mediated mutagenesis can generate mutations which eliminate or reduce the activity of PobR and thereby cause a decreased transcription of *pobA*. There is no

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analysis of whether compound-target interactions can be identified via PCR mutagenesis. The studies in Kok are focused on identifying mutations which cause a loss-of function of a known gene.

Kok does not teach or suggest that it would be desirable or possible to randomly mutagenize the entire chromosome of a bacterium. Nor does Kok teach or suggest the use of PCR products of approximately 10 kb to approximately 15kb. Kok et al. describe a PCR-based technique for targeted random mutagenesis of selected genes in a bacterial chromosome. Kok discloses only mutagenesis of a known 1434 bp region around *pobR*. Kok does state that "[t]he technique is of general interest because it may be widely applicable in mutagenesis of other chromosomal genes." However, this would not suggest to one of skill in the art that PCR-mediated mutagenesis could be used at the chromosomal scale and does not teach or suggest the use of approximately 10 kb to approximately 15 kb DNA fragments to do so.

The Examiner alleges that Minshull et al. provide the teaching of the length requirements lacking in Kok et al. Applicants respectfully traverse the examiners rejection in light of Kok et al and Minskull et al. and request reconsideration.

To establish a *prima facie* case of obviousness under 35 USC §103(a), three basic criteria must be met: 1) The prior art reference must teach or suggest all the claim limitations; 2) There must be some suggestion or motivation to modify the reference or to combine reference teachings; and 3) There must be a reasonable expectation of success. Also, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. MPEP 2142

The present invention as claimed in Claim 5 and dependent claims 10, 11 and 36 involves random mutagenesis of the complete chromosome using PCR to generate large

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DNA overlapping PCR products of approximately 10 kb to approximately 15 kb. The present invention allows for the identification of mutations associated with resistance to a compound that are anywhere on the chromosome. By applying the methods of the present invention, even for compounds for which the mechanism of action is unknown, the user is able to identify genes that, when mutated, result in a decreased susceptibility to a compound. This allows one who is skilled in the art to predict the mechanism of action of any compound with no prior information concerning the molecular target of the compound. Before the disclosure of this invention it had not been shown that a mutation that conferred resistance to a compound could be systematically identified using PCR without prior knowledge of the region with which the compound interacted.

Claims 5 and 6 and those claims dependent thereon are directed to identifying and characterizing mutations that confer resistance to a compound. Minshull et al. does not suggest providing random mutagenesis to encompass the complete chromosome or to use overlapping PCR products of approximately 10 kb to approximately 15 kb. In addition, Minishull et al. do not specifically identify any mutations that confer resistance to a compound, not do they identify the site of any mutation generated. Minshull et al. are concerned with recursive sequence recombination to generate molecular diversity by creating a family of nucleic acid molecules showing substantial sequence identity to each other but differing in the presence of mutations. Minshull et al do not identify the mutations or the site of the mutation and do not suggest that one should do so. The Examiner notes that Minshull et al. may comprise steps of PCR mutagenesis, and comprise the screening of transformants for various functional properties. However, Minshull et al. do not identify the mutation responsible for the resistance as required by the final steps of claims 5 and 6 and the claims dependent thereon.

The prior art does not teach or suggest all the claim limitations of the present invention.

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Neither Kok et al. alone, nor in combination with Minshull et al., teach or suggest to one of skill in the art that PCR mutagenesis could be used over the entire chromosome to identify and locate mutations responsible for resistance to a chemical compound. The present invention, as claimed in amended Claim 5 and dependent claims 10, 11 and 36, involves random mutagenesis of the complete chromosome using PCR to generate large DNA fragments of approximately 10 kb to approximately 15 kb and allows for the identification, anywhere on the chromosome, of mutations which conferring resistance to a compound.

Kok does not teach or suggest that it would be desirable or possible to randomly mutagenize the entire chromosome of a bacterium. Nor does Kok teach or suggest the use of PCR products of approximately 10 kb to approximately 15kb. Kok et al. describe a PCR-based technique for targeted random mutagenesis of selected genes in a bacterial chromosome. Kok discloses only mutagenesis of a known 1434 bp region around pobR. Kok does state that "[t]he technique is of general interest because it may be widely applicable in mutagenesis of other chromosomal genes." However, this would not suggest to one of skill in the art that PCR-mediated mutagenesis could be used at the chromosomal scale and does not teach or suggest the use of approximately 10 kb to approximately 15 kb DNA fragments to do so.

Nothing disclosed in Minshull et al. rectifies the deficiencies of Kok et al. As discussed above, Minshull et al. do not teach or suggest the identification of the mutations or the site of the mutations. Minshull does not disclose any method by which those specific mutations could be identified or characterized. Minshull merely identifies that a mutation has occurred that affects a studied phenotype. Thus, there is no motivation in Minshull et al. to modify the method of Kok et al. to encompass the complete chromosome or to use overlapping PCR products of approximately 10 kb to approximately 15 kb. Even if the references are combined and the PCR mutagenesis method in Kok were applied to identify mutations, neither reference teaches or discloses

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a way in which to identify mutations associated with resistance to a compound and to identify the site of the mutation on the chromosome. In contrast, with the methods of the present invention the user is able to identify genes that when mutated result in a decreased susceptibility to a compound, even for compounds for which the mechanism of action is unknown. This allows one who is skilled in the art to predict the mechanism of action of any compound with no prior information concerning the molecular target of the compound. Before the disclosure of this invention it had not been shown that a mutation which conferred resistance to a compound could be systematically identified using PCR without prior knowledge of the region with which the compound interacted.

There would not have been a reasonable expectation of success

While it may have been obvious to try Kok et al.'s method employing larger PCR products encompassing the complete chromosome of a bacterium to identify mutations that confer resistance to a compound, there would not have been a reasonable expectation of success that such a method would work. This is because, one of skill in the art would not have had a reasonable expectation that that one could search the entire chromosome using PCR and identify one or more mutations conferring resistance to a compound. In other words, before the disclosure of the present invention, it would not have been obvious to generate overlapping PCR products of 10 kb to 15 kb in length, which PCR products would encompass the complete chromosome, and to pool groups of these PCR 10 kb to 15 kb products that correspond to 100 kb of the chromosome to transform wild type bacteria; to isolate strains of the transformed bacteria that were resistant to a compound and to identify the exact mutation and site of the mutation that caused the resistance. In fact, as noted in previous amendments, it would not have been obvious that frequencies of transformation would be high enough to allow for selection of compound resistant mutants where the region or gene containing the mutation was unknown. Kok and Minshall do not suggest to one of skill in the art that such a method would succeed. Minshall provides a method which is very laborious and time consuming. Simply because Kok's described their method as "extremely easy and

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efficient" and Kok suggests that it should be useful in the analysis of a "wide range of chromosomal point mutation", does not suggest its use to prepare and employ larger PCR products encompassing the complete chromosome of a bacterium.

Applicants assert that the Examiner is using hindsight construction, using Applicants' disclosure, to come to the conclusion that Claims 5-6, 9, 22, 24 and 36 are obvious over Kok in light of Minshull. Applicants assert that the data presented in Kok et al and Minshull et al. would not have suggested to one of skill in the art, at the time the instant application was filed, that there was a reasonable expectation for these experiments to work to identify compound resistant mutants where the region or gene containing the mutation was unknown; thus requiring that the entire chromosome be analyzed to account for all possible mutations.

Therefore, neither Kok nor Minshull, taken alone or in combination, teach or suggest all of the limitations of the invention claimed in claims 5 and 6 or those dependent thereon.

In addition, there is no suggestion or motivation to modify the reference or to combine reference teachings. The examiner points to the statement in Kok et al. that their method is "extremely easy and efficient," and that their method should be useful in the analysis of "a wide range of chromosomal point mutations" as long as "a selection for mutations exists". The Examiner states that since the method of Minshull et al. is more labor intensive and time consuming than that of Kok et al. (requiring, e.g., multiple rounds of recombination to product variant products - see, e.g., column 4, line 52- column 5, line 8), an ordinary artisan would have been motivated to have made such a modification for the advantage of more rapidly generating and identifying variants have the properties taught by Minshull et al.. Applicants respectfully traverse this reasoning. Kok et al. limits the analysis to specific genes and does not suggest application of the ir techniques to an entire chromosome. The efficiency provided by Kok is due to the

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limited part of the genome being studied. There would be no expectation that this method could be applied to a very much larger chromosome with any expectation of a successful outcome.

The Examiner's application of Minshull et al. to claims 22 and 24, as disclosing increasing diversity by using "prior methods of mutagenesis" does not teach or suggest the present invention either alone or in combination with Kok et al. as discussed above or with Belland as discussed below. As noted above, Minshull provides no suggestion to use overlapping PCR fragments of the entire chromosome or to identify the specific mutation introduced nor the site of the mutation.

Similarly, the Examiner's application of the combination of Kok and Minshull to claim 36 does not make this claim obvious. The mere fact that Minshull et al. disclose screening for antibacterial activity does not suggest that PCR mutagenesis could be applied to a complete chromosome to generate mutants resistant to a compound or that overlapping PCR products of approximately 10 kb to approximately 15 kb be used to identify a specific mutation and the site of such a mutation.

(13) Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. in view of Minshull et al. as applied to claims 5-6, 9, 22, 24, and 36, above, and further in view of Belland et al. (Molecular Microbiology 14(2):371-382 [1994]). As discussed above, Kok et al. and Minshull et al. taken either alone or together do not teach the methods of the instant claims. Nothing disclosed in Belland rectifies the deficiencies of Kok. The application of Belland and the combination of Belland with Kok has been previously discussed on multiple occasions. Belland discloses using chemical (ciprofloxacin) induced mutagenesis to generate resistant strains and then confines the analysis of those mutants to short regions of the *gyrA* and *parC* genes which had previously been implicated in quinolone resistance. Belland does not disclose the use of PCR to generate mutants. Belland uses PCR amplification of short stretches of DNA

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(<180 bp) to sequence regions of *gyrA* and *par C* to identify mutations. Belland notes that mutations giving rise to ciprofloxacin resistance that occur outside the region analyzed may influence the level of ciprofloxacin resistance but that these mutation would not be detected by the procedures used in Belland (p377, 2nd column, lines 44-48). Belland does not disclose any method by which those mutations could be identified or characterized. Nothing in Belland teaches or suggests that PCR mutagenesis could be applied to a complete chromosome to generate mutants resistant to a compound or that overlapping PCR products of approximately 10 kb to approximately 15 kb be used. Thus, there is no motivation in Belland to modify the method of Kok to encompass the complete chromosome or to use overlapping PCR products of approximately 10 kb to approximately 15 kb. Even if the references are combined and the PCR mutagenesis method in Kok were applied to identify mutations which confer resistance to a compound such as ciprofloxacin, neither reference teaches or discloses a way in which to identify mutations associated with resistance to a compound that are anywhere on the chromosome. Both references deal with selecting for mutations associated with a phenotype for which the region/gene responsible for such phenotype is known. In contrast, with the methods of the present invention the user is able to identify genes that when mutated result in a decreased susceptibility to a compound, even for compounds for which the mechanism of action is unknown. This allows one who is skilled in the art to predict the mechanism of action of any compound with no prior information concerning the molecular target of the compound. Before the disclosure of this invention it had not been shown that a mutation which conferred resistance to a compound could be systematically identified using PCR without prior knowledge of the region with which the compound interacted.

As discussed above, Minshull et al does not provide what is lacking in either Kok or Belland. None of these references provide what is absent in the others to suggest the instant claims.

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The prior art does not teach or suggest all the claim limitations of the present invention.

Neither Kok alone, Minshull et al. alone nor in combination with Belland, teaches or suggests to one of skill in the art that low fidelity PCR mutagenesis could be used over the entire chromosome to locate mutations responsible for resistance to a chemical compound. The present invention, as claimed in amended Claim 5 and dependent claims 10, 11 and 36, involves random mutagenesis of the complete chromosome using PCR to generate large DNA fragments of approximately 10 kb to approximately 15 kb and allows for the identification, anywhere on the chromosome, of mutations which conferring resistance to a compound.

There would not have been a reasonable expectation of success

While it may have been obvious to try low fidelity PCR mutagenesis to identify mutations that confer resistance to a compound, there would not have been a reasonable expectation of success that such a method would work. This is because for the frequencies of transformation expected, one of skill in the art would not have had a reasonable expectation that that one could search the entire chromosome using PCR and identify one or more mutations conferring resistance to a compound. In other words, before the disclosure of the present invention, it would not have been obvious that frequencies of transformation would be high enough to allow for selection of compound resistant mutants where the region or gene containing the mutation was unknown. Kok and Belland do not suggest to one of skill in the art that such a method would succeed. To the contrary, Kok and Belland disclose frequencies of transformation that support the unobviousness of the instant invention.

Applicants assert that the Examiner is using hindsight construction, using Applicants' disclosure, to come to the conclusion that Claims 5 and 10-11 are obvious. Applicants assert that the data presented in Kok et al and Belland et al. would not have suggested to one of skill in the art, at the time the instant application was filed, that there

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was a reasonable expectation for these experiments to work to identify compound resistant mutants where the region or gene containing the mutation was unknown; thus requiring that the entire chromosome be analyzed to account for all possible mutations.

(14) Claims 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. in view of Minshull et al. as applied to claims 5-6, 9, 22, 24, and 36, above, and further in view of Pruna (U.S. Patent No. 5,532,239 [7/1996]).

The references of Kok et al. and Minshull et al. do not teach the method of the instant claim. Pruna teach the antibiotic ciprofloxacin (column 2, lines 33-40). While Minshull et al. suggest screening for resistance to a variety of antibiotics, and disclose the identification of genes conferring increased resistance to the antibiotic moxalactam as discussed above, neither Minshull nor Kok teach or suggest that PCR mutagenesis could be applied to a complete chromosome to generate mutants resistant to a compound or that overlapping PCR products of approximately 10 kb to approximately 15 kb be used. Pruna does nothing to supply the missing motivation.

(15) Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. in view of Minshull et al. as applied to claims 5-6, 9, 22, 24, and 36, above, and further in view of Ibrahim et al (U.S. Patent No. 5,145,667 [9/1992]).

The Examiner notes that the references of Kok et al. and Minshull et al. do not teach the particular compounds of the instant claims, but suggests that Ibrahim et al.'s teaching of the antibiotics triclosan and DHDPE would have made obvious the instant invention. Ibrahim discloses oral hygiene compositions that are useful in the inhibition of dental calculus and further discloses addition of an anti-bacterial compound to the composition to provide anti-plaque activity. Disclosed as suitable anti-bacterial agents are diphenyl ethers and specifically triclosan. Ibrahim has no disclosure relating to a method of mutagenesis or of identifying mutations that confer resistance to a compound.

Applicants do not contest that DHDPE and Triclosan are known antibiotics. The disclosure of Ibrahim, even if it does teach DHDPE and Triclosan, does nothing to make up for the deficiencies of Kok and Minshull. As discussed in detail above, Claim 5 is not

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obvious and therefore claims dependent from it are non-obvious as well. Ibrahim does not disclose PCR-mediated mutagenesis using approximately 10 to approximately 15 kb overlapping fragments encompassing a complete chromosome. And in no way does Ibrahim increase the expectation of success that such a method would succeed even where the compound is triclosan or DHDPE.

(16) Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. in view of Minshull et al. as applied to claims 5-6, 9, 22, 24, and 36, above, and further in view of Wohlstadter (US. Patent No. 6,087,177 [7/11/2000; filed 3/16/1992]). As discussed above, Minshull et al. and Kok taken alone or together do not suggest that PCR mutagenesis could be applied to a complete chromosome to generate mutants resistant to a compound or that overlapping PCR products of approximately 10 kb to approximately 15 kb be used. Neither reference taken alone or in combination teach the identification of a specific mutation or the site of the mutation. Wohlstadter is directed at a rational method for obtaining a novel molecule capable of a desired interaction with a substrate of interest. The disclosure of Wohlstadter is not related to identification of mutations that confer resistance to a compound. Wohlstadter does nothing to make up for the deficiencies of Kok et al. in combination with Minshull. For the reasons given in 15 above, Claim 6 is in compliance with the requirements of 35 USC §103(a), and therefore claims 22-23 which depend from Claim 6 are also in compliance with the requirements of 35 USC §103(a).

For the reasons given above, Applicants believe that all pending claims are in complete compliance with 35 USC §103(a). Applicants respectfully request withdrawal of all Claim rejections under 35 USC §103(a).

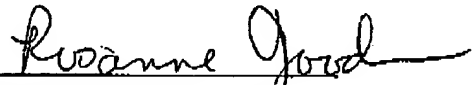
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CONCLUSION

In light of the amendments and remarks made herein, Applicants respectfully request reconsideration and withdrawal of all rejections and objections and request allowance of all the pending claims. Notification to this effect is earnestly solicited. The Examiner is encouraged to contact the Applicants' undersigned attorney to discuss this matter if any questions should arise upon further examination of the pending claims.

Respectfully submitted,

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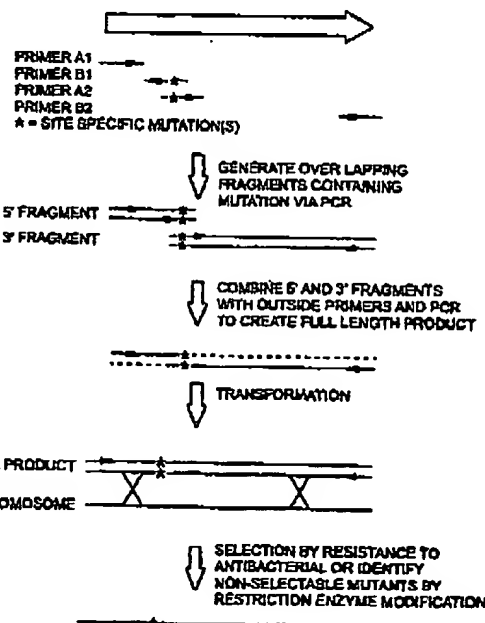
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(54) Title: METHODS OF IDENTIFYING AND CHARACTERIZING MUTATIONS WITHIN BACTERIAL DNA GYRASE AND PAB1

(57) Abstract

The instant invention allows for the simultaneous creation
and identification, or identification of mutations that confer resis-
tance to antibacterial compounds.RAPID GENERATION OF SITE-
SPECIFIC CHROMOSOMAL MUTANTS

-35-

ABSTRACT

The instant invention allows for the simultaneous creation and
identification, or identification of mutations that confer resistance to antibacterial
compounds.

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